

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE

MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PHOSALONE

Chemical Code #000479, Tolerance #263  
SB950-091

May 20, 1987

Revised September 20, 1988, September 19, 1989

I. DATA GAP STATUS

Chronic rat :	Data gap, inadequate study, no adverse effect indicated
Chronic dog :	Data gap, inadequate study, no adverse effect indicated
Onco rat :	No study on file.
Onco mouse :	No data gap, no adverse effect
Repro rat :	Data gap, inadequate study, no adverse effect indicated
Terato rat :	Data gap, inadequate study, adverse effect indicated
Terato rabbit :	No data gap, possible adverse effect
Gene mutation :	Data gap, inadequate study, no adverse effect indicated
Chromosome :	Data gap, inadequate study, no adverse effect indicated
DNA damage :	No study on file.
Neurotox :	No data gap, no adverse effect

-----**Note,**  
**Toxicology one-liners are attached**

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

Index by D. A. Shimer

File name: T890919

Revised: J. Gee, 9/20/88, G. Chernoff, 9/19/89.

Record numbers through volume 263-041 listed by the Pesticide Registration Library have been rectified with those listed in the Toxicology Summary.

## II. TOXICOLOGY SUMMARY

## CHRONIC RAT

018 036256 "Phosalone: Safety Evaluation by Repeated Oral Administration to Rats for 103-104 Weeks." (Woodard Research Corp., 7-27-67) Phosalone, 96.4%, lot 4363B; 30/sex/group were fed 0, 25, 50, or 250 ppm in the diet for 103-104 weeks; onco NOEL > 250 ppm, ChE NOEL = 25 ppm; no adverse effects reported except inhibition of plasma and rbc cholinesterase at 50 and 250 ppm; unacceptable (missing stability, homogeneity and content of diets, no individual histopathology, no clinical chemistry or urinalysis, no clinical observations.) NLH, 10-29-85 and JR(G), 11-15-85. EPA 1-liner: Minimum. Oncogenic NOEL > 250 ppm (HDT), ChE NOEL = 25 ppm (marginal plasma ChE depression.)

005 032722 Short summary of 36256.

025 050836 Analytical information on test material for 36256.

## CHRONIC DOG

024 043793 "Phosalone-Safety Evaluation by Repeated Oral Administration to Dogs for 107 Weeks." (Woodard Research Corp., 9-7-67) Phosalone, 96.4%, lot 4363B; test compound given to beagles in feed at 0, 100, 200, or 1000 ppm for 107 weeks, 4/sex/group; no adverse effect reported; ChE NOEL < 100 ppm, systemic NOEL = 100 ppm (body weight, smooth muscle histopathology in small intestine with increase in amount of basophilic granules in myofibrillar cytoplasm at 1000 ppm, less at 200 ppm; unacceptable (no analyses of diet), possibly upgradeable. JG, 5/18/87. EPA 1-liner: Minimum. NOEL < 100 ppm (LDT) (blood ChE depression.)

005 032723 Short summary of 43793.

025 050836 Analytical information on test material for 43793.

The registrant proposes to conduct a 3 month study in dogs to establish the NOEL for cholinesterase inhibition. Diet analyses will be done in this study. See letter dated February 1, 1988 (no document number) and minutes of the January 22, 1988 meeting at CDFA.

## ONCOGENICITY, RAT

No study on file. A combined rat study will be performed in response to the December, 1987 EPA registration standard. See minutes of January 22, 1988 meeting with CDFA and letter dated February 1, 1988 (no document number).

## ONCOGENICITY, MOUSE

\*\* 019, 025 036257, 050838 "Lifetime Oncogenicity Study in Mice (Phosalone)." (International Research and Development Corp., Report no: 347-009, 6-23-80) Phosalone, 95.3%; groups of 60 or 65 per sex given 0, 15, 50, or 150 ppm in diet for 104 weeks, interim sacrifice of 5/sex in control and high dose at 6 weeks; ChE NOEL < 150 ppm (only control and 150 ppm were assayed), onco NOEL > 150 ppm; no adverse effect for oncogenicity reported; increase in adrenal organ weight but no histopathology noted; no clinical chemistry except for cholinesterase; acceptable as oncogenicity study with submission of 50838, missing pages for 36257. JR(G), 11-15-85 and 5-18-87. EPA 1-liner: Minimum. Oncogenic NOEL > 150 ppm, systemic NOEL > 150 ppm, ChE NOEL < 150 ppm (decreased cholinesterase activity.)

## REPRODUCTION, RAT

020 036258 "Phosalone: Three-Generation Reproduction Study in the Rat (Lot #43638)." (Woodard Research Corp., 9-67) Phosalone, lot 4363B, 96.4%; 10 males/group mated with 2 x 10 (20) females, 3 generations, two litters per generation; fed at 0, 25, or 50 ppm; no adverse effects in reproduction are reported; NOEL  $\geq$  50 ppm; unacceptable (no analyses of diets, no clinical signs reported, no evidence of MTD, excess mortality of F2B parents due to infection, no food consumption recorded.) DAS, 5-12-87 and JR(G), 11-6-85. EPA 1-liner: Minimum. NOEL  $\geq$  50 ppm (systemic and reproduction - HDT)

005 945776 Short summary of 36258.

025 050836 Analytical information on test material for 36258.

A replacement study in rats will be conducted in response to the December 1987 EPA registration standard. See letter dated February 1, 1988 (no document number).

## TERATOGENICITY, RAT

021 036261 "Assessment of the Teratogenic Potential of Piperonyl butoxide, Biphenyl, and Phosalone in the Rat." (Publication in: Toxicol. Appl. Pharmacol. 47:353 (1979), Khera, K. S. et al.)

A phosalone formulation containing 30% (w/w) active ingredient (Zolone PM, lot MAG 438) was administered by gavage to 18 to 20 female Wistar rats at dosages of 0, 12.5, 25, and 50 mg/kg from days 6 to 15 of gestation; NOEL  $\geq$  50 mg/kg. No effect on body weight, no clinical signs; unacceptable, journal article. DAS, 5-12-87 and JR(G), 11-15-85.

EPA 1-liner: Minimum. NOEL = 50 mg/kg/day (teratogenic HDT).

**038 074148** "Embryotoxicity Study (Including Teratogenicity) with Phosalone Technical in the Rat", (Research and Consulting Company AG, 3-21-89). Technical Phosalone, 93.6% pure in 4% carboxymethylcellulose was administered by oral intubation to groups of 25 mated Wistar/HAN female rats at 0, 2, 10, and 20 mg/kg/day on days 6 through 15 of gestation. **Possible adverse effects:** Maternal signs of organophosphate toxicity including continuous chewing motion, piloerection, and dyspnea; decreased food consumption; decreased maternal weight gain; and an increased number and percentage of resorptions all at 20 mg/kg/day. Developmental NOEL = 10 mg/kg (increased embryonic resorptions); Maternal NOEL = 10 mg/kg (signs of organophosphate toxicity; decreased food consumption; decreased weight gain). **Unacceptable**, upgradeable with acceptable review of 1.) the pilot study to justify the dose range tested, 2.) individual maternal data on the time of onset, degree, and duration of clinical signs related to organophosphate toxicity, and

3.) a justification for the deviation from acceptable methods of fixation for Wilson sections.  
(G.Chernoff, 8/22/89)  
No EPA 1-liner.

#### TERATOGENICITY, RABBIT

021 036259 "Study of Teratological Activity of Phosalone (RP 11974) on Chicken Embryos and Rabbits (Study in rabbit)." (Rhone-Poulenc, 2-7-69) Phosalone, purity not stated, lot GD3307; 25 dams/group were given 0, 2, 6 or 18 mg/kg/day by oral capsule, days 6-16 of gestation, thalidomide 100 mg/kg as positive control; no adverse effect reported; NOEL  $\geq$  18 mg/kg/day; unacceptable (dose selection not justified, no purity stated, no MTD, number of corpora lutea not counted, others.)  
DAS, 5-12-87 and JR(G), 11-15-85.

EPA 1-liner: Minimum. NOEL  $\geq$  18 mg/kg/day (HDT).

**\*\* 039 074293** "Embryotoxicity Study (Including Teratogenicity) with Phosalone Technical in the Rabbit", (Research and Consulting Company AG, 4-21-89). Technical Phosalone, 93.5% pure in 4% carboxymethylcellulose was administered by oral intubation to groups of 16 mated Chinchilla (Kfm:Chin) female rabbits at 0, 1, 10, and 20 mg/kg/day on days 6 through 18 of gestation. **Possible adverse effects:** Maternal signs of organophosphate toxicity including dyspnea, abdominal cramps, convulsive behavior; and decreased food consumption at 20 mg/kg/day; an increased percentage of resorptions at 10 and 20 mg/kg/day. Developmental NOEL = 1 mg/kg (increased resorptions); Maternal NOEL = 10 mg/kg (signs of organophosphate toxicity; decreased food consumption). **Acceptable.** (G. Chernoff, 8/22/89)  
No EPA 1-liner.

041 76127 Supplemental evaluation of the incidence of resorptions in the rabbit teratology study 039 074293. No worksheet.

Rabbit Teratology Summary: The initial study submitted for evaluation (record no. 036259) reported no adverse effect and a NOEL  $>$  18 mg/kg/day. In contrast, the replacement study demonstrated a possible adverse effect and resulted in lowering the maternal NOEL to 10 mg/kg/day, and the developmental NOEL to 1 mg/kg/day. Given the limitations of the initial study (unknown purity of the test material; unconventional method of exposure by oral capsules; and lack of an MTD), the results of the better conducted and complete replacement study are considered by CDFA to supercede the results of the initial study. (G. Chernoff, 8/22/89)

#### TERATOGENICITY, CHICK EMBRYO

021 036260 "Study of Teratological Activity of Phosalone (RP 11974) on Chicken Embryos and Rabbits (Study in chicken embryo)." (Rhone-Poulenc, 2-7-69) Phosalone, purity not stated, lot GD3307; 30 fertilized eggs/group, solvent (DMSO) or 0.2, 0.6, or 1.8 mg intravitelline injection; embryos removed on day 18 and examined; no abnormalities or adverse effect on weight reported; unacceptable, not a guideline type study. DAS, 5-12-87 and JR(G), 11-15-85.  
EPA 1-liner: Minimum. NOEL  $\geq$  1.8 mg/egg (HDT).

#### GENE MUTATION

022 036264 "Phosalone (11,974 RP)-Mutagenicity Study on *Salmonella Typhimurium*." (Rhone-Poulenc, report no: 19 234 E, 1-19-78) Phosalone, purity not stated, batch GD4440;

*Salmonella*, use of 4 strains, TA1535, TA1537, TA100 and TA98, by plate incorporation at 0 to 1000 ug with and without rat liver activation, also spot test at 100 ug/10 ul; no increase in revertants reported; unacceptable (no individual data, no positive control for 3 strains, no independent confirming trial, no justification for high concentration and no statement on cytotoxicity.) DAS, 5-12-87 and JR(G), 11-14-85.

EPA 1-liner: No core grade. NOEL > 1000 mg/plate (HDT) (without S-9 fraction; insufficient controls to evaluate results with S-9 fraction.)

Replacement studies with *Salmonella* and CHO/HGPRT assays will be performed - see letter of February 1, 1988.

#### MUTAGENICITY, CHROMOSOME

022 036262, 036263 "Dominant Lethal Study in Mice: Phosalone (36262); Cytosan (36263)." (International Research and Development Corp., report no: 999-013, 12-18-78) Phosalone, 95.3% pure, lot MAG 322; 10 males were given vehicle, 10, 30 or 75 mg/kg by gavage, single dose, and mated with 2 females/week for 8 weeks; cytosan at 40 mg/kg as positive concurrent control gave questionable results - a study run at 60 and 240 mg/kg Cytosan at a later date showed a positive dominant lethal effect in the first 3 weeks; no dominant lethal effect reported; unacceptable (too few animals per group, MTD not reached.) DAS, 5-12-87 and JR(G), 11-14-85.

EPA 1-liner: No core grade. Negative for Charles River CD-1 mice (assay considered inadequate; positive control did not produce mutations, insufficient females for significance, HDT not established as MTD for these mice.)

An *in vitro* cytogenetics assay with CHO cells will be performed in response to the registration standard issued by EPA in December of 1987. See letter dated February 1, 1988 (no document number).

#### MUTAGENICITY, DNA DAMAGE

No study on file. A study of DNA repair in rat hepatocytes will be conducted in response to the EPA registration standard issued in December of 1987.

#### NEUROTOXICITY

\*\* 023 36266 "Acute Delayed Neurotoxicity study in Hens with Phosalone." (Gulf South Research Institute, report no: 411-851-40, 9-22-83) Phosalone, purity not stated, no lot no.; 600 mg/kg to 20 protected hens by gavage; repeat dosing on day 22, LD<sub>50</sub> of 503 mg/kg; TOCP as positive control; 2/20 and 7/18 died in test groups; no evidence of acute delayed neurotox reported; Acceptable. DAS, 5-12-87 and JR(G), 11-14-85.

No EPA 1-liner.